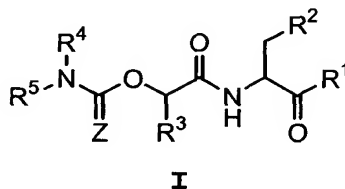


We claim:

1. A method of treating a disease in a patient that is alleviated by treatment with a caspase inhibitor, comprising administering to a patient in need of such a treatment a therapeutically effective amount of a compound of formula I:



- 5 or a pharmaceutically-acceptable derivative thereof,
wherein:
Z is oxygen or sulfur;
R¹ is hydrogen, -CHN₂, -R, -CH₂OR, -CH₂SR, or -CH₂Y;
R is a C₁₋₁₂ aliphatic, aryl, aralkyl, heterocyclyl, or
10 heterocyclylalkyl;
Y is an electronegative leaving group;
R² is CO₂H, CH₂CO₂H, or esters, amides or isosteres
thereof;
R³ is a group capable of fitting into the S2 sub-site of a
15 caspase; and
R⁴ and R⁵ taken together with the intervening nitrogen
form a mono-, bi- or tricyclic hetero ring system
having 1-6 heteroatoms selected from nitrogen, oxygen
or sulfur.

20

2. The method of claim 1 wherein the compound has one or more of the following features:

- (i) Z is oxygen;

- (ii) R^1 is hydrogen, $-R$, $-CH_2OR$, $-CH_2SR$, or $-CH_2Y$;
- (iii) R^2 is CO_2H or an ester, amide or isostere thereof;
- (iv) R^3 is a group having a molecular weight up to 140 Daltons; or
- (v) R^4 and R^5 taken together with the intervening nitrogen form a monocyclic, bicyclic or tricyclic ring system wherein each ring of the system has 5-7 ring atoms.

3. The method of claim 2 wherein the compound has the following features:

- (i) Z is oxygen;
- (ii) R^1 is hydrogen, $-R$, $-CH_2OR$, $-CH_2SR$, or $-CH_2Y$;
- (iii) R^2 is CO_2H or an ester, amide or isosteres thereof;
- (iv) R^3 is a group having a molecular weight up to 140 Daltons; and
- (v) R^4 and R^5 taken together with the intervening nitrogen form a monocyclic, bicyclic or tricyclic heterocyclic or heteroaryl ring system wherein each ring of the system has 5-7 ring atoms.

4. The method of claim 3 wherein R^1 is $-CH_2Y$.

5. The method of claim 4 wherein R^1 is $-CH_2F$ and R^3 is a C_{1-4} alkyl group.

6. The method of claim 5 wherein R^4 and R^5 taken together with the intervening nitrogen form a bicyclic or tricyclic heterocyclic or heteroaryl ring system wherein each ring of the system has 5-7 ring atoms.

7. The method of claim 6 wherein R⁴ and R⁵ taken together with the intervening nitrogen form a tricyclic heterocyclic or heteroaryl ring system wherein each ring
5 of the system has 5-7 ring atoms.

8. The method of claim 7 wherein the middle ring of the tricyclic ring system is a five- or six-membered ring.

10

9. The method of claim 1 wherein the compound has one or more of the following features:

- (i) Z is oxygen;
- (ii) R¹ is -CH₂OR, -CH₂SR, or -CH₂Y;
- 15 (iii) R² is CO₂H or an ester, amide or isostere thereof;
- (iv) R³ is C₁₋₄ alkyl; or
- (v) R⁴ and R⁵ taken together with the intervening nitrogen form a ring selected from indole,
20 isoindole, indoline, indazole, purine, dihydropyridine, benzimidazole, imidazole, imidazoline, pyrrole, pyrrolidine, pyrroline, pyrazole, pyrazoline, pyrazolidine, triazole, piperidine, morpholine, thiomorpholine,
25 piperazine, carbazole, phenothiazine, phenoxazine, dihydrophenazine, dihydrocinnoline, dihydroquinoxaline, tetrahydroquinoline, tetrahydroisoquinoline, dihydronaphthyridine, tetrahydronaphthyridine, dihydroacridine, β-carboline, pyrido[4,3-b]indole, 2,3,9-triazafluorene, 9-thia-2,10-diazaanthracene,
- 30

3,6,9-triazafluorene, thieno[3,2-b]pyrrole, or dihydrophenanthridine.

10. The method of claim 9 wherein the compound has
5 one or more of the following features:

- (i) Z is oxygen;
- (ii) R¹ is -CH₂OR, -CH₂SR, or -CH₂Y;
- (iii) R² is CO₂H or an ester, amide or isostere thereof;
- 10 (iv) R³ is C₁₋₄ alkyl; or
- (v) R⁴ and R⁵ taken together with the intervening nitrogen form a ring selected from indole, isoindole, indoline, indazole, benzimidazole, imidazole, pyrrolidine, pyrazole, triazole,
15 piperidine, morpholine, thiomorpholine, piperazine, carbazole, phenothiazine, phenoxazine, dibenzoazepine, dihydro-dibenzoazepine, dihydrophenazine, dihydrocinnoline, dihydroquinoxaline, tetrahydroquinoline,
20 tetrahydroisoquinoline, dihydronaphthylidine, tetrahydronaphthylidine, dihydroacridine, β-carboline, pyrido[4,3-b]indole, 2,3,9-triazafluorene, 9-thia-2,10-diazaanthracene, 3,6,9-triazafluorene, thieno[3,2-b]pyrrole, or
25 dihydrophenanthridine.

11. The method of claim 10 wherein the compound has one or more of the following features:

- (i) Z is oxygen;
- 30 (ii) R¹ is -CH₂OR, -CH₂SR, or -CH₂Y;
- (iii) R² is CO₂H or an ester, amide or isostere thereof;

(iv) R³ is C₁₋₄ alkyl; or

(v) R⁴ and R⁵ taken together with the intervening nitrogen form a substituted or unsubstituted ring system selected from carbazole, phenothiazine, indole, indoline, 5H-dibenzo[b,f]azepine, 10,11-dihydro-5H-dibenzo[b,f]azepine, β -carboline, pyrido[4,3-b]indole, 2,3,9-triazafluorene, 9-thia-2,10-diazaanthracene, 3,6,9-triazafluorene, thieno[3,2-b]pyrrole, or dihydrophenanthridine.

10

12. The method of claim 11 wherein Z is oxygen; R¹ is -CH₂OR, -CH₂SR, or -CH₂Y; R² is CO₂H or an ester, amide or isostere thereof; R³ is C₁₋₄ alkyl; and R⁴ and R⁵ taken together with the intervening nitrogen form a substituted or unsubstituted ring system selected from carbazole, phenothiazine, indole, indoline, 5H-dibenzo[b,f]azepine, 10,11-dihydro-5H-dibenzo[b,f]azepine, β -carboline, pyrido[4,3-b]indole, 2,3,9-triazafluorene, 9-thia-2,10-diazaanthracene, 3,6,9-triazafluorene, thieno[3,2-b]pyrrole, or dihydrophenanthridine.

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13. The method of claim 12 wherein R¹ is -CH₂Y.

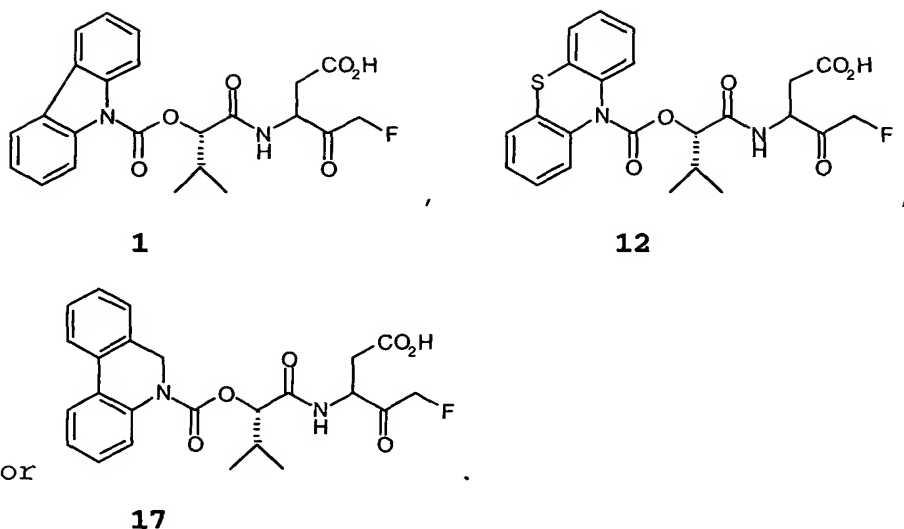
14. The method of claim 11 wherein R¹ is -CH₂F.

25

15. The method of claim 1 wherein the compound is selected from those compounds listed in Table 1.

16. The method of claim 1 wherein the compound is selected from the following:

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17. The method according to any of claims 1-16 wherein the disease or treatment is selected from an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a disease associated with cell death, an excess dietary alcohol intake disease, a viral mediated disease, uveitis, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, scarring, graft vs host disease, organ transplant rejection, osteoporosis, leukemias and related disorders, myelodysplastic syndrome, multiple myeloma-related bone disorder, acute

myelogenous leukemia, chronic myelogenous leukemia,
metastatic melanoma, Kaposi's sarcoma, multiple myeloma,
haemorrhagic shock, sepsis, septic shock, burns,
Shigellosis, Alzheimer's disease, Parkinson's disease,
5 Huntington's disease, Kennedy's disease, prion disease,
cerebral ischemia, epilepsy, myocardial ischemia, acute
and chronic heart disease, myocardial infarction,
congestive heart failure, atherosclerosis, coronary
artery bypass graft, spinal muscular atrophy, amyotrophic
10 lateral sclerosis, multiple sclerosis, HIV-related
encephalitis, aging, alopecia, neurological damage due to
stroke, ulcerative colitis, traumatic brain injury,
spinal cord injury, hepatitis-B, hepatitis-C,
hepatitis-G, yellow fever, dengue fever, or Japanese
15 encephalitis, various forms of liver disease, renal
disease, polyaptic kidney disease, H. pylori-associated
gastric and duodenal ulcer disease, HIV infection,
tuberculosis, meningitis, a treatment for complications
associated with coronary artery bypass grafts, or an
20 immunotherapy for the treatment of various forms of
cancer.

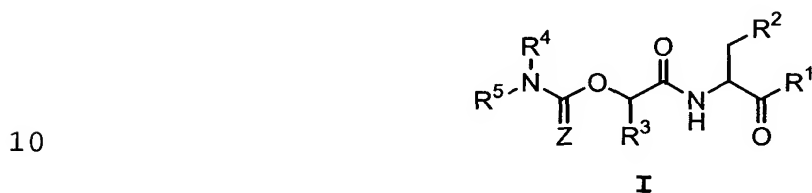
18. The method according to any of claims 1-16
wherein the compound is used to treat complications
associated with coronary artery bypass grafts.

19. The method according to any of claims 1-16
wherein the compound is used for the preservation of
25 cells, said method comprising the step of bathing the
cells in a solution of the compound or a pharmaceutically
acceptable derivative thereof.

20. The method according to any of claims 1-16 wherein the compound is used for an organ transplant or for preserving blood products.

5 21. The method according to any of claims 1-16 wherein the compound is used as a component of immunotherapy for the treatment of cancer.

22. A compound of formula I:



or a pharmaceutically-acceptable derivative thereof, wherein:

Z is oxygen or sulfur;

15 R¹ is hydrogen, -CHN₂, -R, -CH₂OR, -CH₂SR, or -CH₂Y;

R is a C₁₋₁₂ aliphatic, aryl, aralkyl, heterocyclyl, or heterocyclylalkyl;

Y is an electronegative leaving group;

R² is CO₂H, CH₂CO₂H, or esters, amides or isosteres

20 thereof;

R³ is a group capable of fitting into the S2 sub-site of a caspase; and

R⁴ and R⁵ taken together with the intervening nitrogen form a mono-, bi- or tricyclic hetero ring system

25 having 1-6 heteroatoms selected from nitrogen, oxygen or sulfur.

23. The compound of claim 22 wherein the compound has one or more of the following features:

- (i) Z is oxygen;
- (ii) R¹ is hydrogen, -R, -CH₂OR, -CH₂SR, or -CH₂Y;
- (iii) R² is CO₂H or an ester, amide or isostere thereof;
- 5 (iv) R³ is a group having a molecular weight up to 140 Daltons; or
- (v) R⁴ and R⁵ taken together with the intervening nitrogen form a monocyclic, bicyclic or tricyclic ring system wherein each ring of the system has 5-
10 7 ring atoms.

24. The compound of claim 23 wherein the compound has the following features:

- (i) Z is oxygen;
- 15 (ii) R¹ is hydrogen, -R, -CH₂OR, -CH₂SR, or -CH₂Y;
- (iii) R² is CO₂H or an ester, amide or isosteres thereof;
- (iv) R³ is a group having a molecular weight up to 140 Daltons; and
- 20 (v) R⁴ and R⁵ taken together with the intervening nitrogen form a monocyclic, bicyclic or tricyclic heterocyclic or heteroaryl ring system wherein each ring of the system has 5-7 ring atoms.

25 25. The compound of claim 24 wherein R¹ is -CH₂Y.

26. The compound of claim 25 wherein R¹ is -CH₂F and R³ is a C₁₋₄ alkyl group.

30 27. The compound of claim 26 wherein R⁴ and R⁵ taken together with the intervening nitrogen form a bicyclic or

tricyclic heterocyclic or heteroaryl ring system wherein each ring of the system has 5-7 ring atoms.

28. The compound of claim 27 wherein R⁴ and R⁵ taken
5 together with the intervening nitrogen form a tricyclic heterocyclic or heteroaryl ring system wherein each ring of the system has 5-7 ring atoms.

29. The compound of claim 28 wherein the middle
10 ring of the tricyclic ring system is a five- or six-membered ring.

30. The compound of claim 22 wherein the compound has one or more of the following features:

- 15 (i) Z is oxygen;
(ii) R¹ is -CH₂OR, -CH₂SR, or -CH₂Y;
(iii) R² is CO₂H or an ester, amide or isostere thereof;
(iv) R³ is C₁₋₄ alkyl; or
20 (v) R⁴ and R⁵ taken together with the intervening nitrogen form a ring selected from indole, isoindole, indoline, indazole, purine, dihydropyridine, benzimidazole, imidazole, imidazoline, pyrrole, pyrrolidine, pyrroline,
25 pyrazole, pyrazoline, pyrazolidine, triazole, piperidine, morpholine, thiomorpholine, piperazine, carbazole, phenothiazine, phenoxazine, dihydrophenazine, dihydrocinnoline, dihydroquinoxaline, tetrahydroquinoline,
30 tetrahydroisoquinoline, dihydronaphthyridine, tetrahydronaphthyridine, dihydroacridine, β-carboline, pyrido[4,3-b]indole, 2,3,9-

triazafluorene, 9-thia-2,10-diazaanthracene,
3,6,9-triazafluorene, thieno[3,2-b]pyrrole, or
dihydrophenanthridine.

- 5 31. The compound of claim 30 wherein the compound
has one or more of the following features:
- (i) Z is oxygen;
 - (ii) R¹ is -CH₂OR, -CH₂SR, or -CH₂Y;
 - (iii) R² is CO₂H or an ester, amide or isostere
10 thereof;
 - (iv) R³ is C₁₋₄ alkyl; or
 - (v) R⁴ and R⁵ taken together with the intervening
nitrogen form a ring selected from indole,
isoindole, indoline, indazole, benzimidazole,
15 imidazole, pyrrolidine, pyrazole, triazole,
piperidine, morpholine, thiomorpholine,
piperazine, carbazole, phenothiazine, phenoxazine,
dibenzoazepine, dihydro-dibenzoazepine,
dihydrophenazine, dihydrocinnoline,
20 dihydroquinoxaline, tetrahydroquinoline,
tetrahydroisoquinoline, dihydronaphthyridine,
tetrahydronaphthyridine, dihydroacridine, β-
carboline, pyrido[4,3-b]indole, 2,3,9-
triazafluorene, 9-thia-2,10-diazaanthracene,
25 3,6,9-triazafluorene, thieno[3,2-b]pyrrole, or
dihydrophenanthridine.

32. The method of claim 31 wherein the compound has
one or more of the following features:
- 30 (i) Z is oxygen;
 - (ii) R¹ is -CH₂OR, -CH₂SR, or -CH₂Y;

(iii) R^2 is CO_2H or an ester, amide or isostere thereof;

(iv) R^3 is C_{1-4} alkyl; or

(v) R^4 and R^5 taken together with the intervening
5 nitrogen form a substituted or unsubstituted ring
system selected from carbazole, phenothiazine,
indole, indoline, 5H-dibenzo[b,f]azepine, 10,11-
dihydro-5H-dibenzo[b,f]azepine, β -carboline,
pyrido[4,3-b]indole, 2,3,9-triazafluorene, 9-thia-
10 2,10-diazaanthracene, 3,6,9-triazafluorene,
thieno[3,2-b]pyrrole, or dihydrophenanthridine.

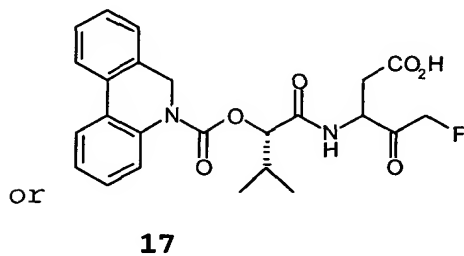
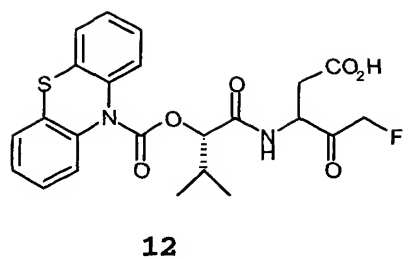
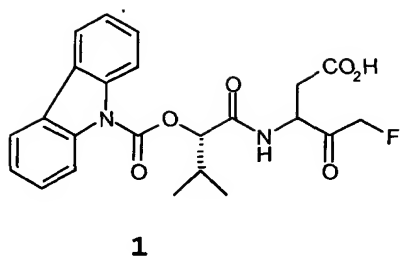
33. The method of claim 32 wherein Z is oxygen; R^1
is $-\text{CH}_2\text{OR}$, $-\text{CH}_2\text{SR}$, or $-\text{CH}_2\text{Y}$; R^2 is CO_2H or an ester, amide
15 or isostere thereof; R^3 is C_{1-4} alkyl; and R^4 and R^5 taken
together with the intervening nitrogen form a substituted
or unsubstituted ring system selected from carbazole,
phenothiazine, indole, indoline, 5H-dibenzo[b,f]azepine,
10,11-dihydro-5H-dibenzo[b,f]azepine, β -carboline,
20 pyrido[4,3-b]indole, 2,3,9-triazafluorene, 9-thia-2,10-
diazaanthracene, 3,6,9-triazafluorene, thieno[3,2-
b]pyrrole, or dihydrophenanthridine.

34. The compound of claim 33 wherein R^1 is $-\text{CH}_2\text{Y}$.
25

35. The compound of claim 34 wherein R^1 is $-\text{CH}_2\text{F}$.

36. The compound of claim 22 wherein the compound
is selected from those compounds listed in Table 1.
30

37. The compound of claim 22 wherein the compound
is selected from the following:



5

38. A pharmaceutical composition comprising a compound according to any of claims 22-37 and a pharmaceutically acceptable carrier.